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The action of light on the retina: Translation and commentary of Holmgren (1866)

Running head: Holmgren and the electroretinogram

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Abstract

In 1866 Holmgren published an account of the physiological action of light on the retina. The article is taken as the origin of research on the electroretinogram although the term was not introduced until much later. We present a translation of the article into English and provide a commentary on its reception and significance.

Keywords: Holmgren, light, retina, electroretinogram, Dewar, McKendrick

> It would be of great importance to find a method that would give, if possible, a direct and objective expression for the effect of light on the retina. The following is an attempt to solve this problem. (Holmgren, 1866, p. 178)

Introduction

On 19th January, 1866 the Swedish physiologist Frithiof Holmgren (1831-1897) delivered a lecture at the Upsala Medical Society (to which he belonged) that was published in the January 1866 issue of *Upsala Läkareförenings Förhandlingar* (Proceedings of the Upsala Medical Society). In his lecture Holmgren presented evidence of electrical activity in the visual pathway as a consequence of light falling on the retina. In his obituary, Tigerstedt (1897) wrote: “These represent the first observations of functional changes in the nervous end-organs of peripheral sensory organs, and will secure the name of Holmgren an honourable place in physiology for all time” (p. vii). Despite its significance in the history of neuroscience, we are not aware of any published translation of the article into English. It appeared in the first volume of the journal which covered the years 1865-1866 and its date is often given as 1865 rather than 1866. It became known more widely when attention was directed to it after similar observations had been published by Dewar and McKendrick (1873) but in ignorance of Holmgren’s prior publication.

Holmgren’s (1866) article was the harbinger of research on electrical responses to light in the visual system. It did not, however, record the action of light in the retina but from the optic nerve. His later article (Holmgren, 1871) did record what later was referred to as the ‘electroretinogram’; the term was not coined until 1924 by Kahn and Löwenstein. They stated: “By the term “*Elektroretinogramm*” (*Erg*) we mean the curve of the course of the electrical potential differences in the retina of the *intact* animal registered photographically when the exposure changes” (Kahn & Löwenstein, 1924, p. 304). The second article

(Holmgren, 1871) was also in Swedish but a short summary of it in German was provided by Rabl-Rückhard (1871a, 1871b). Holmgren (1880) gave an extended account of the studies in German under the title of the retinal current; Holmgren had demonstrated to his satisfaction that the source of the electrical currents induced by light was the retina. The 1880 article was probably written in the mid-1870s because reference is made to Dewar and McKendrick's experiments but not to his own later work (Holmgren, 1878) on retinal currents. It would appear that McKendrick's (1874) acknowledgement and accounts of it in German journals broadened the influence of Holmgren's work. Granit refers to the experiments by Dewar and McKendrick as being "unjustly neglected" and states that "Dewar and McKendrick (Dewar, 1877) were the first to record potential changes from the human eye" (Granit, 1947, p. 350).

Alarik Frithiof Holmgren (Fig. 1) was appointed as the first professor of physiology at the University of Upsala in 1864. His interests in the action of nerves derived from periods spent in Du Bois Reymond's laboratory in 1863 and 1864, and a visit to Helmholtz in 1869 stimulated his fascination with colour vision (Tigerstedt, 1897). Holmgren carried out wide-ranging research on vision (Lindberg, 2015); he is also known for his work on microstimulation of the retina (Norrsell, 2010) and for the introduction of colour vision tests for railway workers (Mollon & Cavonius, 2012). A biography was written by Nobel Laureate, Ragnar Granit (1964) who applied the electroretinogram extensively in his studies of retinal colour mechanisms.

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Fig.1 about here

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Holmgren's article was one of 13 articles and book reviews he contributed to the volume, as is evident from Fig. 2. In particular, among the articles presented before that on the electrical activity of the retina, there are two somewhat connected to the themes of this study:

one on the movements of the iris under the action of miotic or mydriatic and agents (respectively atropine or 'kalabar', this being a plant extract containing physostigmine) and another entitled *Centripetal nerve stimulus in motor nerves*.

We provide here an annotated translation into English of the article on the electrical retinal response to light which is not verbatim but stays close to the original written in old Swedish in order to reflect Holmgren's somewhat halting style. Problems were encountered with some of the specialist terms that do not have ready equivalents in modern English. Holmgren's article did not contain any footnotes but we have added some in order to clarify terms or concepts as well as to provide an historical context of the significance or otherwise of Holmgren's text.

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Figure 2 about here

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Translation

Holmgren F (1866): Method to obtain objective evidence of the effect of light on the retina. *Upsala Läkareförenings Förhandlingar 1*: 177-191.

Referring to his planning of a method to obtain objective evidence of the effect of light on the retina, Mr. Holmgren announced the following:

Like every type of exact research on nature, physiological research constantly seeks, wherever possible, to find methods whose purpose is to replace subjective perception, which is always uncertain, with objective phenomena and precise measurements.

Without any doubt, it would not look good in the science of senses if one would not use the resources that the subjective method has, but it is equally clear that this method is only useful in experiments with humans.[1] If we could not find an objective method, then we are obliged to leave unused the rich material that the animal kingdom has to offer.[2] This is of particular concern to the physiology of higher senses.

In the case of how light affects the retina, there is so far no other indicator than subjective perception. It is true that the movements of the iris and its changes with accommodation, are in some way, expressions of the effect of light, but these are not always present and thus cannot be taken as the outcome of such effects.

Therefore it would be of great importance to find a method that would give, if possible, a direct and objective expression for the effect of light on the retina. The following is an attempt to solve this problem.

The important work in the area of animal electricity by Du Bois Reymond, in many ways so fruitful, has taught us that each nerve, no matter what it connects together, only works in one way. It is by leading or starting a molecular process that is called nerve action [“*innervation*” in the original] or the principle of the nerve movement. This process, that might be caused by an impulse from a peripheral nerve ending or from a central ganglion cell,[3] or by some direct stimulation somewhere in the middle of an intact nerve trunk,

1 The problem of subjectivity and objectivity in science (as well as other areas) has a long history and is multifaceted. With regard to the theme of Holmgren’s article, particularly worthy of mention are the considerations made by Luigi Galvani (1737-1798) in the foreword to an unpublished essay on his experiments on animal electricity dated 1782. Galvani justifies his decision to study the involvement of electricity on muscular motion, rather than on sensation, because “the motion manifests itself to the eyes of the observer” whereas “the sensation, even though it makes itself sensible to the person experiencing it, is – on the other hand – totally hidden from the observer” (see Piccolino and Bresadola, 2014).

2 In his time, Holmgren could not foresee the developments of the behavioural and conditioning techniques allowing scientists to study sensation in animals. Indeed, at the same time Frans Cornelis Donders (1818-1889; 1869a, 1869b) reported his investigations on measuring the duration of mental processes by means of reaction times.

3 Ganglion cell (“*Gangliicell*” in the original) was a generic expression used to indicate the nervous cell before the enunciation, in the 1890s, of the neuron doctrine, at a time in which there was no clear understanding of the relation of the body of nerve cells with the nerve fibres, and – moreover – on the way nerve cells communicate with them.

expresses itself electrically in the negative variation of the nerve current. This assumption has been taken as a general law although it has not been shown experimentally that it takes place inside the optic nerve when light strikes the retina.

Thus it would be interesting to test experimentally the optic nerve in this regard, in order to find new support for the above mentioned law and, at the same time, to be able to define the effect of light on retina.

The experiment would consist of deriving the electric current from the optic nerves toward a sensitive galvanometer and observing the changes that might take place when the light strikes the retina. If one considers initially the chances of success that this trial seems to promise, it is clear that the obvious difficulties concentrate around two things.

One of these difficulties is to find a preparation that meets the physiological and technical demands for the success of this experiment – in other words an optic nerve that, at the same time, can keep its functional ability and which is long enough so that it is possible to record the current from two points that are not too close to each other.[4] A priori, there is no reason to assume that the optic nerve would be less viable than the other nerves in an organism. One should be able to hope, that among animals whose nerves can keep their physiological qualities alive for a relatively long time when separated from the organism, one could even find an optic nerve that meets these demands.[5] The so-called cold-blooded animals should be able to meet the above mentioned condition. If one chooses among these animals, in order to meet the second condition one must leave apart the usual experimental animal, the frog, because its optic nerve is relatively insignificant in its length and diameter, and should instead choose a somewhat bigger species of fish. In this respect, the common

4 The technique used by Emil Du Bois Reymond (1818-1896) to record his "negative variation" ("*negative Schwankung*" in the original) was based on the use of macroscopic electrodes and, moreover, it needed the use of relatively long stumps of nerve in order to get sizeable electrical responses of the nervous activity.

5 As we remark in the introduction, in doing his experiments Holmgren aimed at obtaining the electric response of the optic nerve, not of the nervous elements of the retina.

pike (*Esox lucius*) meets all the minimal demands. This fish weighs about 15 pounds [6 kg] and one can easily obtain from it an optic nerve that has, from the bulb to the proximal section, a length of 10 mm and thickness of 3 mm in diameter.[6] This preparation thus seems to have the qualities that make the trial possible.

The other difficulty is to find a galvanometer that is sensitive enough to be able to measure carefully the expected changes in the nerve current. If one only wants to find out whether the nerve current can be brought to display the negative fluctuation by the action of the light on retina, an ordinary multiplier of 20,000 coils should be sufficient for this purpose, supposing that one has a nerve of such dimensions as the above mentioned. This was of course one of the tasks of the experiment but it was as well, once achieved, only a necessary means to solve the actual problem. If one expects to find subtler changes in the current that could be interesting and important, one would need an instrument where the magnet follows and reflects the current more closely than the relatively blunt *Nobili* pair of needles in their slow and steady oscillations.[7]

This last requirement could most probably be achieved with the Wiedemann mirror galvanometer on the condition that it is endowed with a magnet, light weight and mobile, so that it could show those weak currents that we would expect here.[8] Meeting this requirement also brings about the greatest difficulty. As we know, the steel magnet is also a mirror and the size of the area of the mirror needs to be decided, so a decrease in weight is gained at the expense of the thickness. The fixing of a completely flat surface on a thin piece of steel introduces incredible technical difficulties. For one year I negotiated with numerous

6 The great length of the optic nerve in some fishes had been noticed since the second half of the 17th century by the Italian anatomist Marcello Malpighi as reported in his *Opera Posthuma*, first published in London in 1697.

7 Leopoldo Nobili (1784-1835), an important Italian physicist, had built up in 1825 a sensitive galvanometer based on a particular arrangement of two magnetic needles which made the measuring device independent from the influence of the static earth magnetism (“astatic galvanometer”). This device was relatively slow in its response, and, because of its great sensitivity, was subject to oscillations. With this device Carlo Matteucci was the first to provide in 1839 a physical measurement of animal electricity (see Finger band Piccolino, 2011; and Piccolino and Wade, 2012).

8 This galvanometer, devised by Gustav Heinrich Wiedemann (1826-1899), an important German physicist, was based on a modification of the mirror galvanometer initially designed by Johann Christian Poggendorff.

instrument manufacturers in this country as well as abroad, until I finally managed to get a mirror from F. Sauerwald in Berlin that is 20 mm in diameter and weighs 2 grm.[9]

An experiment was made with this magnet suspended by means of a simple cocoon fibre in the Wiedemann galvanometer. Because there was no other animal preparation available, frogs eyes were used. Du Bois Reymond's familiar amalgamated zinc vessel, with zinc vitriol, filter paper and containers of plastic clay were used as non-polarising electrodes to conduct the current to the galvanometer. Because the frog's optic nerve has such small dimensions, no significant current can be expected; that is why I undertook to conduct the current, on the one hand from the optic nerve tightly cut at the bulb, and on the other hand from the edge of the cornea, so that the opening of the pupil was over the edge of the clay and exposed for the action of light. When using this kind of current derivation, a deviation of 50-60 lines is achieved on the measurement scale with the distance between this scale and the mirror which I am now using. When using this kind of current derivation the cornea stays positive against the severed optic nerve or the back pole of bulb. If instead one derives the current on the one hand from the back part of bulb, and on the other hand from some cross-section of the optic nerve, the latter stays positive against the former and an effect of 5-10 lines on the scale can be achieved.[10]

If one now uses the more effective of these arrangements [i.e. that from the back of the bulb to the cornea] and allows the light to suddenly fall into the pupil that was first covered, the magnet produces an effect of about 5 lines towards the positive direction and

9 F. Sauerwald was an important instruments maker of Berlin, who fabricated galvanometers widely used in Germany (for instance by Du Bois Reymond) and in other countries of Europe. The particular instrument used by Holmgren in his retinal experiments, which was built in 1865, is now housed in the Museum of Medical History at Uppsala University and it is illustrated in Lindberg (2015).

10 As already remarked, Holmgren's intention in doing these experiments was to record the electric response of the optic nerve and not of the nervous elements inside the retina. The arrangement with one of the electrodes on the cornea was "more effective" because the main source of currents was precisely inside the eye. The fact that the current polarity decreased, and – even more – that it changed polarity when the electrode was on the posterior pole of the eye instead than on the cornea, was an important indication to the retinal origin of the recorded current. However, in the course of these experiments Holmgren failed to be aware of this notion. As we shall see, the only other possible source of electric current that he considered – and tried to exclude experimentally - was that possibly due to muscular events correlated to variation of the pupil size.

then eventually goes back to its original position. The same happens if one suddenly covers the eye that was beforehand exposed to light. Even in this case one sees an equally big, if not a bigger effect, also towards the positive direction, and afterwards the magnet eventually reaches its original position in the same slow way.[11]

If one uses the weaker arrangement [i.e. the derivation from the back of the bulb toward a transverse section of the optic nerve] the same happens, but the effect is much smaller, almost unnoticeable, and goes towards the negative direction. I should mention this, because of the weak currents one can obtain in this arrangement; I have only once managed to observe the latter phenomenon and that is why, although I am convinced of its correctness, I mention it with some reservation.

Under these circumstances it is of course necessary first to try to answer the question whether, when using the condition of the more effective experimental arrangement, it was indeed the light entering and exiting the eye that caused the activity in the nerve elements of the retina or not.

If one studies one of the preparations to determine the sources from which the recorded current might originate, it can be assumed that it could be from the muscles in the eyeball, namely the iris and ciliary muscles. In order to answer this question one must investigate whether the muscles in the iris are activated by the light falling on the eye. I have become convinced that when using light, for example sunlight, it is the light of the rays, and not the heat associated with them, that causes the effect observed; the effect is the same when I let light come through a glass with parallel surfaces whereas no effect was observed when beaming heat was directed to the eye.

11 Holmgren correctly points out to responses of similar polarities to both the onset of a light stimulus and to the offset of a steady light, thus revealing ON-type and OFF-type electric responses to light. In a different experimental conditions Volta had been able to show ON and OFF visual responses at the end of the 18th century induced respectively by the application or the interruption of a circuit made by a bimetallic arc (see Piccolino, 2000; Piccolino & Bresadola, 2014)

For light to be able to cause constrictions in any of the muscle groups of the iris, a reflex or a direct stimulus is needed. As to the former possibility, it must be considered that a large number of investigations carried out recently have revealed the presence of many microscopic nerve cells in the eye bulb which could account for it. If instead one wishes to assume a direct stimulation as an explanation for the effect, then this would amount to supposing that the iris muscles are the only ones endowed, as far as I know, with the property of reacting directly to light, a characteristic that is absent in other muscles.[12] In this regard, the iris of the eel (*Muraena anguilla*) must be particularly sensitive because, even when extracted from the eye, it constricts when light is shone into the eye. Whatever is the case, it is not possible to give an explanation of this phenomenon at the moment.

If one only considers what actually happens, there should be no doubt that even in the eye that has been extracted from the orbit, the pupil constricts when light is shone into it and widens again when light is extinguished. One can easily and reliably convince oneself, as I have found most advantageous, by removing both eyes from one frog and placing them so that one eye is turned towards light, like a window, and the other one is turned away from it. If one then after a while examines both pupils one can see that the one that was turned towards the light is clearly smaller than the other one. If one now, as a control and to convince oneself, switches the places for the eyes, one will find after a while that the pupils have now switched also their sizes, so that the previously dilated, i.e., the one which was away from the light turned eye, is now constricted, and the other one has done the opposite. The evidence is obvious and no more is needed.

12 As we now know, in the retina of various vertebrates - including fishes and amphibians - the fibres of the ciliary muscles are endowed with a photosensitive pigment of the rhodopsin type, and are directly sensitive to light. As a consequence, they can contract even in the enucleated eye and the movement occurs independently from the intervention of nerve fibres, even though nerves may control the contraction state by regulating the intracellular calcium concentration (see Rubin and Nolte, 1984 and references therein). Reactions of the pupil to light in enucleated eyes had been initially reported in the first half of the 19th century by the French physiologist Charles Brown-Séquard (1817-1894). Brown-Séquard showed that in the enucleated eye of the frog and of the eel the pupil reacts to direct illumination, whereas it does not change size when the light is directed exclusively to the retina. Holmgren seems to be unaware of Brown-Séquard's experiments, which were first presented at the French Academy of Sciences in the séance of 4th October 1847.

When one has thus established the effect of light on the iris in an eye that has been extracted from the animal, whatever the reason might be, this should give strong support for the assumption that this is the basis for the changes revealed by the galvanometer. I don't, however, think so. The change in the current that the galvanometer reveals is sudden and does not keep up with the slow movements of the muscles in the iris, but has disappeared long before these movements have come halfway. As a matter of fact, the positive deflection cannot reasonably come from a current fluctuation during the constriction as it could be otherwise assumed. If the current fluctuation is coming from the muscles at work in the iris, then it should originate during the phase of the latent stimulation. But in that case it should go toward the negative direction, by considering what we know about the changes in the currents from the muscles and what I have tried to show previously. It is certainly true that we have no knowledge about the changes that the currents in the smooth muscles at work go through, although it is not probable that the smooth ones in this respect would behave differently from the striated muscles. There is, however, no reason to doubt such similar behaviour between two types of muscle.

Considering the previously mentioned experimental arrangement leading to weaker current recordings, i.e., the one in which the current was conducted on the one hand from a cross-section in the optic nerve and on the other hand from the back part of the eye bulb, the current from the muscles in the iris should not have anything to do with the change. If it can be shown, as I have once seen, that in such an arrangement, the light shone on the retina - or its disappearance - causes a negative fluctuation, then this is in agreement with everything one knows about the laws of the nerve current changes.

But how could we then be able to explain why the change is positive in the arrangement that we have called stronger? Actually, the explanation should not be difficult to provide. If we consider that the original current in the stronger arrangement has an opposite direction compared to the weaker arrangement, and further that the fluctuation caused by light on the eye has a positive direction in relation to the former but a negative one in relation to the latter, the conclusion will obviously be that the current fluctuation in both cases has the same absolute direction.

This finding must at first sight seem confusing for our concepts if we assume that we deal with the same nerve current. We have previously taken for granted that the nerve current alone matters in the weaker arrangement. While on the other hand, this cannot be the case with the stronger arrangement. In this case, the ciliary muscle and the muscles in the iris are within the circuit and the idea, that it is from these organs the considerable increase in power and also the direction of the new current comes from, is not unwarranted.

If one assumes this, everything can be explained easily and unproblematically. The current from the muscles in the eye bulb must be stronger (both results show this) and thereby shows a stronger change. The muscle current, that can be assumed to have an opposite direction to the nerve current, not only compensates this so that its effect completely disappears, but it manifests its remaining surplus of electromotor power in the galvanometer. This manifestation, the result of two streams going in opposite directions, shows a direction opposite to the nerve current.[13]

If one shines light on the retina and assumes that this does not affect the muscle current but instead puts the nerve current into a negative fluctuation, this fluctuation which manifests itself in the decreasing power of the nerve current, must behave like an addition to the muscle current. But because this now determines the direction of the total current, it is clear that a negative fluctuation in the nerve current must manifest itself on the galvanometer as a positive fluctuation on the whole. This is also, as we have seen, what actually happens.

13 Holmgren does not consider that the reason why the current has an opposite polarity in the two arrangements (the stronger and the weaker) may not have to do with what he indicates as “muscle current”, but is generated by the nervous elements of the retina. This is surprising in view of his previous statement that the galvanometer deflection induced by the light stimulus has a faster time course than the contraction of the iris muscles.

If our assumption is correct, then the explanation is given too, and there is support for the view that the current fluctuation observed is a genuine expression for an optic nerve stimulation caused by the light shone on the retina.

My only previous observations that I think need to be controlled and confirmed further are the phenomena that occur with the "the weaker arrangement". Du Bois Reymond says namely that any point at the eye bulb surface stays positive, in an electromotor sense against, with respect to the optic nerve cross-section (*Untersuchungen über thierische Elektricität* Bd. II p. 256). My observations seem to go completely against this as far as the point is on the back segment of the bulbi. It is possible that some source of error that I have not properly observed has caused this result; this being remnants of the muscle or similar, but on the other hand it looks like Du Bois Reymond has never derived the current from any other part of the eye bulb than from some area of the cornea; in which case our observations are completely in agreement. Nevertheless, in this instance in the main results he has not thought about the current from the intra-ocular muscles, but explains the direction of the current – which remains the same even when one of the tips of the conductive metallic arc is applied on the optic nerve cut lengthwise instead of crosswise – in the way that the termination of the nerve in the retina cannot be considered as its natural cross-section.[14]

I hardly need to point out that the explanation for these and related phenomena becomes both more natural and easier, and agrees better with the theory, if one assumes a

14 Du Bois Reymond's model of electrophysiological phenomena was based on the assumption that nerve and muscle fibres are made of an orderly arrangement of electric molecules which would be perturbed by natural or artificial excitation. Despite its historical importance, this model was largely faulty and led the author (and his followers) to accentuate the importance of steady differences of electric potentials between the external surfaces of parts of the animal bodies, which were often of artifactual nature. The expression used here by Holmgren ("natural cross-section") is part of Du Bois Reymond's terminology. It was referred normally to the tendinous extremities of a muscle, or to the termination of a nerve, which were supposed to be negative with respect to the surface of muscle body or nerve trunk. This is false in both cases, whereas it is true that the cut section of a muscle or nerve is negative with respect to the intact external surfaces. As we now know this is due to the fact that the section represents a low resistance communication with the interior of muscle and nerve fibres, which is negative with respect to the extracellular compartment (see Finger & Piccolino, 2011; Piccolino & Bresadola, 2014).

current from the above mentioned muscles; such current should better be assumed even from the theoretical point of view.

That the current fluctuation observed when light is shone into the eye arises from the optic nerve and not from the iris becomes even more probable because the magnet reacts so visibly even to the slightest changes in the intensity of light, like when thin cloud passes over the solar disc in case one works in the sunlight etc. Such sensitivity can be attributed to the retina, but only with great difficulty to the iris, which in the frog eventually completely (and as far as one can see, without oscillations in the steady progress) constricts the pupil when this is turned towards the light (and the reverse when turned toward the dark).[15]

Under favourable circumstances this current fluctuation can be observed for hours after the eye has been extracted. That could give us a reason to oppose the idea that the current would originate from the retina which must be a highly delicate organ with a highly transient functional ability etc. The muscles of the iris, however, could be trusted with a longer life. But one should remember, no matter how delicate the retina might be, that as long as the eye bulb is intact, it is as well-protected as in the eye attached to the organism. It exists in a condition that should only slightly differ from the normal physiological state of a living frog, especially because the life process of this animal is, on the whole, rather torpid. The objection above is thus probably less applicable to the retina than to most of the other organs whose functions could be studied outside the organism. This is also a great advantage, considering the possibilities that the method, here referred to, has to offer.

The previous discussion in all its details (which are motivated by its importance for the main purpose) should by all means speak for the view that the signal observed on the

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15 As it is apparent from these passages, Holmgren is obviously aware that the retina is the place where the visual process begins but he does not realize that the retina itself is the main source of the electric potential he is recording. Possibly, he is misled by the assumption, current at his time, that the initial cells of the retinal layers - and particularly the photoreceptors - were not genuinely nerve cells, and – by consequence - the visual process might not express itself at their level with an electric signal.

galvanometer comes from a spreading variation of the current in the optic nerve. I can come up with one more additional reason for this, based on direct experiments. I have, in my previous lecture, mentioned the observation made by Bidder that upon curare poisoning, the pupils of a frog dilated so extensively that only a thin line of the iris was visible. I have had an opportunity to confirm that.[16] The phenomenon is caused by a paralysis of the motor nerve fibres innervating the pupillary sphincter. With an eye like that, one would not need to worry about a motion in the iris when light is shone into the eye. Even if the frog is placed so that the eyes are turned directly to the sun the pupils should stay dilated. If an eye like that is used in the experiment here in question, there should be no current signal in the galvanometer like the one normally observed, in case that the signal comes from the constriction of the muscles in the iris. But should that occur in a similar fashion, then the signal could be a sign of a stimulation in the optic nerve, because it is most probable, that like other centripetal nerves, the optic nerve is not paralysed by curare. The experiment does not show the slightest difference with respect to what I have described above. The signal is, in its size and form, completely similar to what a fully normal eye brings about. This gives further support to our assumption about the nature and meaning of the signal.

To be able to gain decisive evidence beyond any reasonable doubt one must derive the current from an optical nerve alone, cut crosswise or lengthwise. The eye of the frog is not useful for that purpose because its short optic nerve is cumbersome to handle and also because it produces a weak current. One needs to use fish eyes. So far I have only conducted two experiments and both without success. I used the eyes of a burbot (*Lota vulgaris*) weighing 5 pounds and a pike weighing 15 pounds. The optic nerve of the former whose

16 Holmgren is here alluding to the research on the control of ciliary muscles carried out by the Baltic physiologist Georg Friedrich Bidder (1810-1894) that he had discussed in an article published in two parts in the same issue of the *Upsala Läkareförenings Förhandlingar*. In a paper published the year before, Bidder had shown that in frogs, and also in some mammals, curare could induce dilatation of the pupil (Bidder, 1865). This phenomenon, which was later demonstrated also in reptiles and birds, is consistent with the presence of striated fibres in the ciliary muscles of some animals. It contrasts with the behaviour of the human pupil, which is made exclusively of smooth muscle and is insensitive to the direct application of curare (see Wudka & Irving, 1954).

length is more than enough, is however thin and gave a weak current, whereas that of the latter one was both long and relatively robust and gave a strong current.[17] Light shone on the retina did not, however, give any noticeable signal in either. This was not due to the new arrangement for deriving the electrical current because there was no signal even when one of perpendicular foot points of the arc was on the cornea like previously.[18]

One should look for a reason for the missing effect in the general condition of the fish used. They had been in contact with air a relatively long time and then kept in a somewhat confined container in which they indeed moved and breathed but quite faintly, like a dying rather than a lively fish does. This is the same if one uses eyes from frogs that are in a similar dying condition. The difficulty of obtaining fish fully alive has so far stopped me from completing the experiment referred to here.

If we now assume, on the basis of what have been shown, that those results that have been gained with frog eyes, prove what they should and give a promise of a successful enterprise, one should ask what has been gained and what the method is good for.

If we agree that the explanation for the observations is correct, it is obvious, if that new experience is gained, this being that the light stimulus on the retina puts the optic nerves

17 Although the above passages are somewhat obscure, it is very likely that the currents to which Holmgren is alluding here (weak in the burbot and strong in the pike) are the steady currents normally recorded in the resting condition between the transverse section and the lateral surface of any nerve trunk. With the arrangement of the time, involving large-sized electrodes, it was necessary to have a relatively long nerve stump to appropriately record these currents. To a large extent their intensity depended on the size of the nerve.

18 An apparent paradox emerges here in Holmgren's experiments, i.e. no current is induced by the light stimulation of the retina in the relatively long optic nerves of the fish, whereas – as he had previously shown - some current is recorded in the short nerve of the frog with both electrodes on the nerve (his "weaker arrangement"). This is not surprising, in view of modern knowledge of the time course of electric responses induced by visual stimulation. Holmgren's galvanometer was not fast enough to record the action currents of the optic nerve, which have a duration of about one millisecond, whereas it was sufficient to record the waves of the electroretinogram, and particularly its slower components (these have duration of the order of hundredths of milliseconds and have also a d.c. components for stimuli of long duration). In the case of the frog, the shortness of the optic nerve obliged him to put one of the recording electrodes in close proximity to the eye globe. Consequently, he was able to record light induced currents in frogs, even though they were of small amplitude compared to the situation with one of the two electrodes on the cornea (this one being his 'stronger arrangement'). However, the fact that in the fishes there was no response even when the eye was included in the circuit, suggests that the preparations were not viable in both the burbot and pike. This is consistent with what Holmgren writes in the following passages and explains why he kept working exclusively with frogs.

in a state of spreading excitation and creates a negative variation in its current. This gives new support to the law of Du Bois Reymond on changes in the nerve current during nerve activity. It is so much more value as this concerns one of the nerves of the higher senses and the stimulus is of the kind that for the particular nerve is called adequate.

We see further in these experiments, that it is not only when the light suddenly strikes the retina that the optic nerve is put into a state of activation but even when the light suddenly disappears; in a similar fashion when the electric current is either terminated or started, since, as Du Bois Reymond has shown, the electric current only stimulates the nerve upon a rapid variation in its intensity.

Further, it has been shown that the magnet returns to its original position only relatively slowly, whether the change was caused by light or by its disappearance. This might perhaps be associated with the characteristic of the retina to keep the light sensation for some time after the cause for it has ceased. If one varies light with darkness in succession the magnet's return to its rest position can be delayed further. This way of stimulating corresponds to the tetanizing of other nerves.[19]

This shows, however, that the variation in the movements of the magnet is possible with variations of the stimulus, which sounds promising for the method itself; at the same time it supports our assumptions about the nature of the phenomenon observed.

It was now part of my next plan to try to study the changes caused on the retina by lights of different colours. For that purpose I constructed a camera of cardboard, coated with black paper. One of its gable ends had twin walls; in the middle of them both there was a round opening of 1 ½ inches in diameter – these openings sitting carefully aligned opposite to one another. A round cardboard disc with 8 similar openings at equal distances from one

19 Holmgren's interpretation on this point is correct and is – moreover – consistent with previous experiments made by Volta who showed that the repetitively making and breaking of a circuit made by a bimetallic arc applied to the eye could produce a continuous light sensation in human eye (see Piccolino, 2000; Piccolino & Bresadola, 2014).

another can be with a crank turned between these walls so that one after another, these openings come in the middle of the opening in the wall. The distance between two openings in the disc is so big that the piece in between completely covers the opening in the wall. It is possible in this way by turning the disc, as one wishes, both shine light into the camera and completely shut it out. If one now uses the same zinc vessel and places the experimental eye on its clay container so that the light directly falls on the opening of the pupil, one can in a convenient way both shine light into the eye and shut it out. In order to be able to use lights of different colours, I was thinking of placing flat glass of different colours in the openings in the disc. Lacking that, I used oiled paper of different colours to cover them – this was of course a quite imperfect and even an unsuitable substitute, because this matter allows diffused light to pass, refracting according to the laws, which was not considered. Also, this trial did not in this form give any result.

The best way to achieve the intended purpose is without any doubt to separate light into different colours from the same source using a prism and study their effect on the retina. This is my forthcoming plan which I have so far not been able to realise.

The idea that is behind these endeavours and has brought about this method is the following. It is known that ether oscillations, whose wavelengths do not exceed certain limits on both sides of spectrum (in other words those belonging to the solar spectrum and situated between the Frauenhofer lines A and H), have, in a singular and still unknown way, to evoke a movement in the elements of the retina, in its nature similarly unknown, which in turn transfer this excitation movement to the optic nerve. This in turn manifests itself as a negative variation in the nerve current.[20] There is a whole chain of powers in this process of which one controls the first link – a light of a certain and known wavelength – and the last link can

20 As is clear from this statement, Holmgren does not seem to consider the possibility that the light stimulus might initiate an electrical process at the level of the nervous elements inside the retina, prior to the optic nerve.

directly be read off on the galvanometer – the negative variation. Within this range of combination it should be possible, like from an equation, to solve the unknown middle link – or if that cannot be managed, by comparing the utmost extremes to find something constant and for the science useful relationship between them.

There is an assumption about the former that is not that far away. It is known that there exists an analogous relationship with the hearing organ, namely that air oscillations, whose wavelength and frequency move within certain limits and can be transmitted from the eardrum and through the labyrinth fluids etc., to the ends of the auditory nerve. The ingenious hypothesis by Helmholtz has given us the very probable idea that every element in the organ of Corti has a certain frequency of its own or is, so to speak, tuned to a certain simple tone.

Could we now think that there would exist an analogous relationship with the elements of the retina, e.g., cones and rods and possibly with others that they would each react only to ether oscillations of a certain wavelength but not to others? This idea is not new; it is the same idea that was first proposed by Young and has later on again been supported by Helmholtz. It seems to me that the method proposed here could be suitable to examine this hypothesis.

But it would be even more important if one could find some constant relationship between ether oscillations and nerve electricity, between the wavelengths of the light and the deviating effect of the electric current on the magnet. Its importance is obvious and it is not impossible that it could be found in this way.

The suggestions that I have hinted at are probably a bit wild. They are not meant to be more than untested hypotheses – and cannot therefore mislead anybody. The hypothesis in this form can only give impetus to the research and possibly be a guide but nothing else.

It is possible that the method that I have described here will not lead to those results that it now seems to promise to me. Anyway, it has in it something valuable even though the circumstance that it is based on is new for the science, namely the change in current in the optic nerve when light is shone into the retina. It is not common that one introduces a method before it has been proved to be useful, and has obtained the results that could be obtained with it. If I now have made an exception to that rule, it is only because I believe that information, no matter how small it is, can never come too early.

Commentary

The long history of research on vision has been dominated by descriptions of phenomena. This subjective dimension was combined with objective records when instruments for the measurement of stimuli and responses to them were devised in the 19th century (see Wade, 1998). Initially the instruments controlled the presentation of stimuli (like stroboscopic discs and stereoscopes) and later attention was directed at behavioural responses (like reaction time). In 1860 Gustav Theodor Fechner published his *Elemente der Psychophysik* containing the formulation of the two famous law of psychophysics relating the magnitude of the stimulus to the intensity of the sensation it induced (now known as Weber's and Fechner's laws). In 1865, the Austrian philosopher and physicist, Ernst Mach, published his fundamental work on the lateral interaction in the retina which contained the description and psychophysical analysis of the illusory dark and light bands later to be named after him as 'Mach bands'. Nonetheless, these methods were still dependent upon behavioural responses from the observer.

Attempts to elicit sensations from electrical stimulation of the human eye were made by Volta (1800) with his newly invented battery (see Piccolino, 2000). Volta had earlier carried out studies of galvanic light figures in the 1790s, and also found that intermittent stimulation produced longer lasting effects than constant stimulation (Piccolino & Bresadola, 2014). Volta described how he applied electrical stimulation to the eyes; he connected wires from a battery between the mouth and conjunctiva of the eye, which resulted in the experience of light, even in a dark room. Moreover, he noted that the visual sensation was associated with the onset and offset of the current, and a continuous impression of light could be produced by rapid alternation of polarity. These observations stimulated many researchers, particularly in Germany, to search for other means of distinguishing between ‘subjective’ and ‘objective’ aspects of sensation. For example, Ritter (1801) and Pfaff (1801) applied electrical stimulation to the skin and suggested that there were temperature receptors, as did Weber (1846); this approach was refined by Blix (1884), a student and colleague of Holmgren in Uppsala. Indeed, both Bell (1811) and Müller (1843) enlisted electrical stimulation of the sense organs as a source of support for their notions of specific nerve energies (Wade, 2003). In addition, Purkinje (1823, 1825) wrote two books on ‘Vision in its subjective aspects’ in which he argued that all subjective experiences are accompanied by objective (physiological) causes. Galvanic stimulation of the eye was one of the techniques he employed.

Holmgren’s research heralded the onset of physiological recording in sensory physiology and from that time the term ‘objective’ became synonymous with ‘physiological’. He was strongly inspired by the work of Du Bois Reymond, who had been the first to provide a physical measurement of the electric activity of nerves and Holmgren pursued the possibility that optic nerves could also produce detectable electric currents. The significance of Holmgren’s article was cemented by Granit (1933): “Our knowledge of the retinal action currents, discovered by the Swedish physiologist Holmgren… in 1865, has proceeded hand in hand with the development in electrophysiology in general” (p. 207). Holmgren commenced his article with the hope that an objective record of the effect of light on the retina could be found. This he achieved and the article is taken as the first to demonstrate the electroretinogram, even though electroretinography in the proper sense was only initiated after the application, in the first decades of the 20th century, of methods capable of revealing the rapid time course of retinal electrical potentials and allowing for their graphic recording. As we have remarked, however, in publishing the results of his research, Holmgren (1866) seemed to be unaware of the possibility that the electric events he was recording could actually originate in the retina.

Appreciation of this achievement was not immediate. Indeed, when Holmgren (1871, 1878, 1880) returned to the topic of retinal currents, first in Swedish and later in German, he remarked that the 1866 publication elicited little interest until Dewar and McKendrick were informed of it by a Swedish lady! In 1874 McKendrick wrote:

> …it has come to our knowledge that the subject of the action of light on the retina had been investigated previous to the publication of our paper, by H. Fr. Holmgren, a distinguished Swedish physiologist. We have read his papers published in the "Upsala Lakerefórenings Fórhandlingar." It was with pleasure we at once acknowledged that he has the claim of priority in observing an electrical fluctuation by the action of light, and that his memoirs were valuable contributions to science. It is, however, almost needless to state that our work was done in entire ignorance of any previous observations on the subject, and that our methods of experiments, the delicacy of our instrument, and the distinct numerical data obtained, have enabled us to prosecute the matter in various new directions. (1874, p. 36)

Later research on the electroretinogram has been reviewed by Granit (1947). His book contains a copy of a letter from McKendrick to Holmgren on 20 April 1874 indicating that he and Dewar became aware of Holmgren’s work after they had conducted their initial experiments. Dewar and McKendrick extended the research on physiological action of light on the retina, initiated by Holmgren, even though their initial investigations were conducted in ignorance of it (Dewar, 1877a, 1877b; Dewar and McKendrick, 1873; McKendrick, 1874).

Holmgren spent the year from August 1869-1870 at Helmholtz’s laboratory in Heidelberg where he developed his interests in colour vision generally and colour blindness in particular. This raised the possibility of linking electrical activity in the retina to the wavelength of the light stimulating it, as was suggested in the article written on his return to Uppsala (Holmgren, 1871). It could have been the stimulus for Willy Kühne inviting Holmgren to provide a summary of his research in German (Holmgren, 1880); moreover, Kühne himself was involved in similar experiments with frogs and rabbits and expressed his indebtedness to Holmgren (Kühne and Steiner, 1880). Kühne was the successor to Helmholtz at Heidelberg and saw the advantages of linking Holmgren’s investigations to his own on the chemistry of vision. Following Boll’s (1877/1977) pioneering work Kühne (1879/1977) extracted rhodopsin from the rods of frogs and rabbits and showed that the rate of bleaching was dependent not only on the intensity of light but also on its wavelength. Holmgren’s (1878) subsequent research with frogs and rabbits failed to find any relationship between the retinal currents and visual purple (see Lindberg, 2015). Tigerstedt (1897) described Holmgren’s scientific life as having two phases. The first, from around 1865-1878, was concerned with general physiology with specific reference to the electrophysiology of vision. Thereafter the second phase concentrated on human colour blindness and colour theories (see Mollon & Cavonius, 2012; Norrsell, 2010). Most of his publications were in Swedish.

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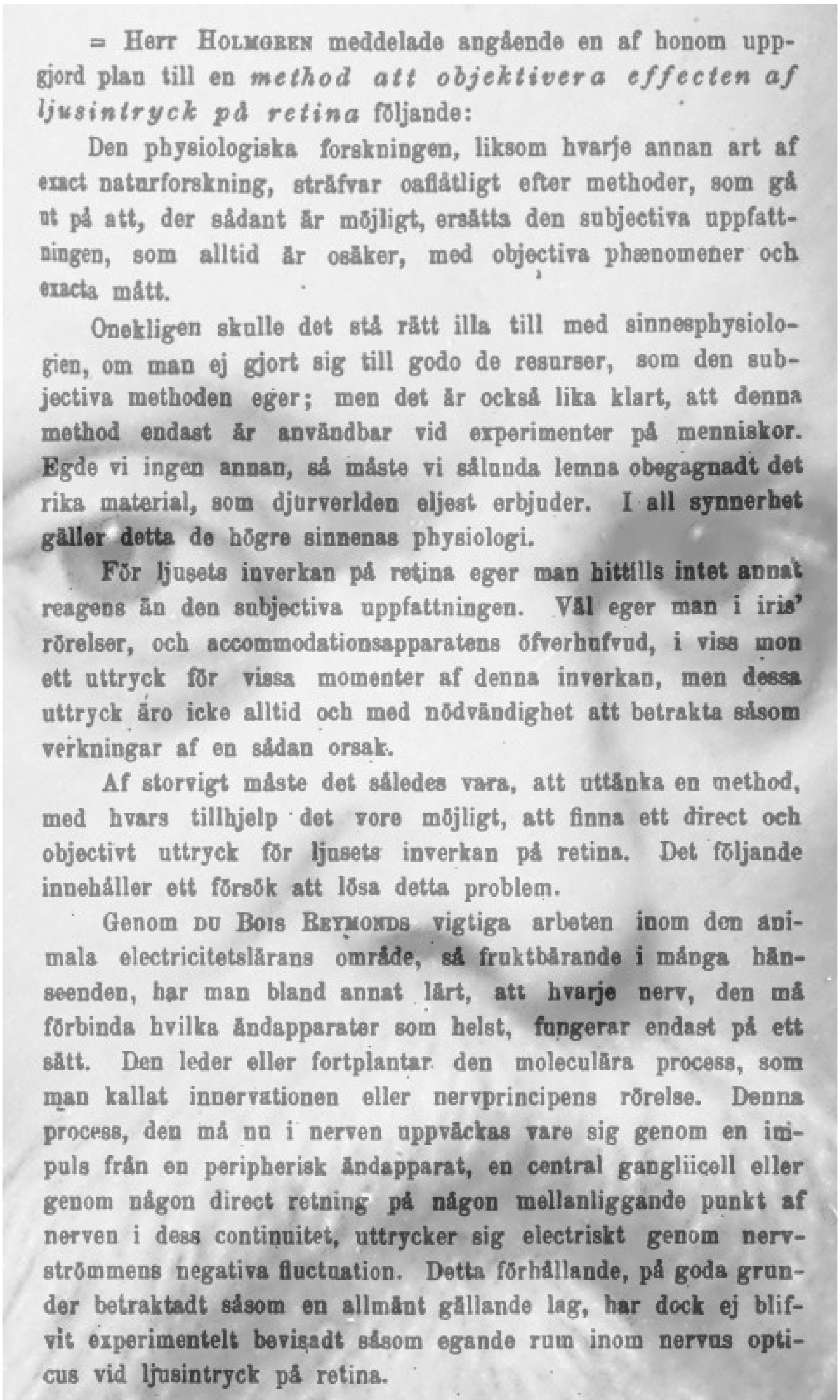
Figure captions

Figure 1. *Holmgren's insight* by Nicholas Wade. The opening paragraphs from Holmgren (1866) combined with his portrait.

Figure 2. *Holmgren's scope* by Nicholas Wade. Holmgren's portrait is combined with the titles of the articles and book reviews that he contributed to the 1865-1866 volume of *Upsala Läkareförenings Förhandlingar.*

Figures



= Herr HOLMGREN meddelade angående en af honom uppgjord plan till en *method att objektivera effecten af ljusintryck på retina* följande:

Den physiologiska forskningen, liksom hvarje annan art af exact naturforskning, sträfvar oaflåtligt efter methoder, som gå ut på att, der sådant är möjligt, ersätta den subjectiva uppfattningen, som alltid är osäker, med objectiva phænomener och exacta mått.

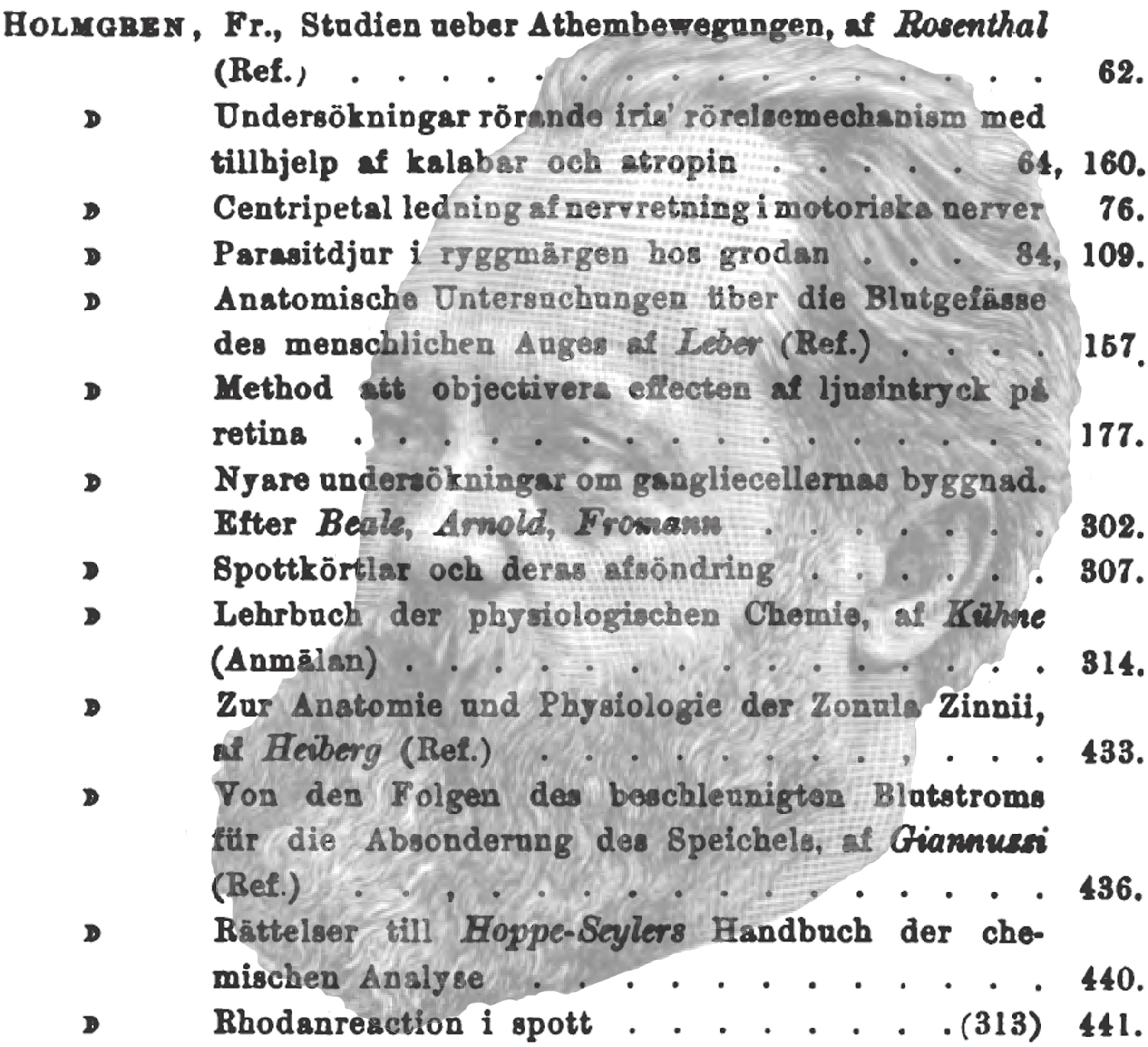
Onekligen skulle det stå rätt illa till med sinnesphysiologien, om man ej gjort sig till godo de resurser, som den subjectiva methoden eger; men det är också lika klart, att denna method endast är användbar vid experimenter på menniskor. Egde vi ingen annan, så måste vi sålunda lemna obegagnadt det rika material, som djurverlden eljest erbjuder. I all synnerhet gäller detta de högre sinnenas physiologi.

För ljusets inverkan på retina eger man hittills intet annat reagens än den subjectiva uppfattningen. Väl eger man i iris' rörelser, och accommodationsapparatens öfverhufvud, i viss mon ett uttryck för vissa momenter af denna inverkan, men dessa uttryck äro icke alltid och med nödvändighet att betrakta såsom verkningar af en sådan orsak.

Af storvigt måste det således vara, att uttänka en method, med hvars tillhjelp det vore möjligt, att finna ett direct och objectivt uttryck för ljusets inverkan på retina. Det följande innehåller ett försök att lösa detta problem.

Genom DU BOIS REYMONDS vigtiga arbeten inom den animala electricitetslärans område, så fruktbärande i många hänseenden, har man bland annat lärt, att hvarje nerv, den må förbinda hvilka ändapparater som helst, fungerar endast på ett sätt. Den leder eller fortplantar den moleculära process, som man kallat innervationen eller nervprincipens rörelse. Denna process, den må nu i nerven uppväckas vare sig genom en impuls från en peripherisk ändapparat, en central gangliicell eller genom någon direct retning på någon mellanliggande punkt af nerven i dess continuitet, uttrycker sig electriskt genom nervströmmens negativa fluctuation. Detta förhållande, på goda grunder betraktadt såsom en allmänt gällande lag, har dock ej blifvit experimentelt bevisadt såsom egande rum inom nervus opticus vid ljusintryck på retina.

Figure 1.



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» Centripetal ledning af nervretning i motoriska nerver 76.
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Figure 2.